

University of Groningen

Target-Controlled Infusion of Cefepime in Critically Ill Patients

Jonckheere, Stijn; De Neve, Nikolaas; Verbeke, Jan; De Decker, Koen; Brandt, Inger; Boel, An; Van Bocxlaer, Jan; Struys, Michel M. R. F.; Colin, Pieter J.

Published in:
Antimicrobial Agents and Chemotherapy

DOI:
[10.1128/AAC.01552-19](https://doi.org/10.1128/AAC.01552-19)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Final author's version (accepted by publisher, after peer review)

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Jonckheere, S., De Neve, N., Verbeke, J., De Decker, K., Brandt, I., Boel, A., Van Bocxlaer, J., Struys, M. M. R. F., & Colin, P. J. (2020). Target-Controlled Infusion of Cefepime in Critically Ill Patients: single center experience. *Antimicrobial Agents and Chemotherapy*, 64(1), [ARTN e01552-19]. <https://doi.org/10.1128/AAC.01552-19>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

1 **TITLE PAGE**

2 Title: Target Controlled Infusion of cefepime in critically ill patients: single center experience

3

4 Stijn Jonckheere, PharmD^{1,2,3}, Nikolaas De Neve, MD⁴, Jan Verbeke, MD⁴, Koen De Decker, MD⁴, Inger

5 Brandt, PhD, PharmD¹, An Boel, PharmD¹, Jan Van Bocxlaer, PhD, PharmD³, Michel M.R.F. Struys, PhD,

6 MD^{2,5}, Pieter J. Colin, PhD, PharmD^{2,3}

7

8 ¹Department of Clinical Microbiology, OLV Hospital Aalst (Belgium); ²Department of Anesthesiology,

9 University Medical Center Groningen, University of Groningen (The Netherlands); ³Laboratory for Medical

10 Biochemistry and Clinical Analysis, Faculty of Pharmaceutical Sciences, Ghent University (Belgium);

11 ⁴Department of Anesthesiology and Intensive Care Medicine, OLV Hospital Aalst (Belgium); ⁵Department of

12 Basic and Applied Medical Sciences, Ghent University (Belgium)

13

14 Corresponding author: stijn.jonckheere@yperman.net, Tel: +3257357327, Fax: +3257357329, Address:

15 Department of Clinical Microbiology, OLV Hospital Aalst, Moorselbaan 164, 9300 Aalst, Belgium.

16

17 Trial registration: Belgium registration number: B126201626975. ClinicalTrials.gov database: NCT02688582

18

19

20

21

22

23

24

25

26

27

28

29

30

31 **ABSTRACT**

32 Attainment of appropriate pharmacokinetic-pharmacodynamic (PK-PD) targets for antimicrobial treatment is
33 challenging in critically ill patients, particularly for cefepime, which exhibits a relative narrow therapeutic-toxic
34 window compared to other beta-lactam antibiotics. Target Controlled Infusion (TCI) systems, which deliver
35 drugs to achieve specific target drug concentrations, have successfully been implemented for improved dosing of
36 sedatives and analgesics in anesthesia. We conducted a clinical trial in the Intensive Care Unit (ICU) to
37 investigate the performance of TCI for adequate target attainment of cefepime. Twenty-one patients treated per
38 standard of care with cefepime were included. Cefepime was administered through continuous infusion using
39 TCI for a median duration of 4.5 days. TCI was based on a previously developed population PK model
40 incorporating the estimated creatinine clearance based on the Cockcroft-Gault formula as input variable to
41 calculate cefepime clearance. A cefepime blood concentration of 16 mg/L was targeted. To evaluate the
42 measured versus predicted plasma concentrations, blood samples were taken (median of 10 samples per patient)
43 and total cefepime concentrations were measured using UPLC-MS/MS. Performance of the TCI system was
44 evaluated using the Varvel criteria. Half (50.3%) of measured cefepime concentrations were within $\pm 30\%$
45 around the target value of 16 mg L⁻¹. The wobble was 11.4%, median prediction error (MdPE) was 21.1%,
46 median absolute prediction error (MdAPE) was 32.0%, and divergence was -3.72%.h⁻¹. Based on these results
47 we conclude that TCI is useful for dose optimization of cefepime in ICU patients.

48

49 **KEYWORDS:** Target Controlled Infusion, drug infusion system, cefepime, pharmacokinetics, Intensive Care
50 Unit

51

52

53

54

55

56

57

58

59

INTRODUCTION

Inappropriate dosing of antibiotics is a driver for antimicrobial resistance development (1), acute toxicity (2,3) and poor clinical outcome (4-5). This is particularly true for cefepime, a fourth generation cephalosporin, which has shown to exhibit a narrow therapeutic-toxic window (2-3,6). Defining adequate dosing regimens in critically ill patients is challenging as pharmacokinetics (PK) in these patients are known to vary considerably (7-14) and these patients are more likely to be infected by less susceptible bacteria (12).

Traditionally, dosing of antibiotics is based on nomograms which define a dosing regimen based on one or a limited set of patient covariates. In the critically ill, these nomogram-based dosing regimens frequently result in a significant proportion of patients not achieving the therapeutic target (13). Hence, treatment should be individualized using therapeutic drug monitoring and/or population PK (PopPK) models. In recent years several software packages were developed that allow model-based treatment individualization (14). Whilst therapeutic drug monitoring (TDM) linked with Bayesian forecasting provides a powerful opportunity for delivering individualized care for patients (15), several issues in current strategies for dose optimization of antimicrobials have hindered clinical implementation in most ICU's (16,17).

Target-controlled infusion (TCI) is a technique of continuously infusing intravenous drugs and is mainly known in the field of anesthetics (18). TCI allows the clinician to target a predefined concentration in a specific body compartment or tissue of interest. The computer then calculates the optimal infusion rate required to achieve this user-defined target concentration as fast as possible without overshooting the target, based on a PopPK model and patient specific covariates (e.g. age, weight, serum creatinine, etc.) which are integrated in the model. An on-line coupled infusion pump then delivers this optimal infusion regimen to the patient. In comparison to the aforementioned manually controlled infusions, TCI systems might provide a more convenient and performant alternative. Treatment individualization is made easy as the PopPK model and associated covariates are embedded in the TCI devices. Dose adaptations are not limited to practicable changes in infusion rates, dose strengths, dosing intervals, etc. but TCI continuously calculates and adjust the infusion rate to exactly match the distribution and elimination kinetics of the drug during treatment.

In this prospective pharmacokinetic study, we evaluated the performance of a cefepime TCI system in a cohort of critically ill patients. Furthermore, the additional PK data was used to update the earlier presented PopPK model for cefepime (19).

RESULTS

Twenty-one critically ill patients were included in this study. Patients received cefepime for the following indications: suspected or documented respiratory infection (18 of 21; 86%), abdominal infection (1 of 21; 5%), combined respiratory and abdominal infection (1 of 21; 5%) or infection of unknown origin (1 of 21; 5%). Microbiological samples taken before cefepime treatment identified in 16 of 21 (76%) patients one or more pathogens: *Klebsiella* spp. (n = 8), *Escherichia coli* (n = 6), *Citrobacter* spp. (n = 2), *Proteus mirabilis* (n = 1), *Pseudomonas aeruginosa* (n = 1), *Morganella morganii* (n = 1) and *Enterobacter cloacae* (n = 1), *Staphylococcus aureus* (n = 1) and *Haemophilus influenzae* (n = 1). MIC values for cefepime ranged from ≤ 1 mg L⁻¹ to 4 mg L⁻¹ (75th percentile: ≤ 1 mg L⁻¹). Table 1 shows the clinical characteristics of the study patients.

The median treatment duration with TCI was 4.0 days (IQR: 2.0 – 5.0 days) and daily cefepime dose was 1.8 g (IQR: 1.6 – 2.5 g) at day 1, 1.3 g (IQR: 1.1 – 2.2 g) at day 2, 1.3 g (IQR: 1.1 – 2.0 g) at day 3 and 1.3 g (IQR: 1.1 – 1.9 g) at day 4. During treatment, a median of 10 blood samples were taken per patient (IQR: 9 – 11) leading to a total of 201 samples. The median of the measured cefepime plasma concentrations was 19.2 mg L⁻¹ with an inter-quartile range of 15.3 to 23.3 mg L⁻¹ (the mean and SD were 19.5 and 6.36 mg L⁻¹, respectively). The percentage of measured concentrations within ± 10 , 20, 30, 40 and 50% of the 16 mg L⁻¹ target were 20.7, 36.2, 50.3, 66.3 and 77.7%, respectively. Figure 1 shows the measured cefepime concentrations and the predicted concentrations according to the TCI system. The average performance metrics (Varvel criteria) in this patient cohort were: MdAPE: 28.7 %, MdPE: 20.3 %, Wobble: 12.2 %, Divergence: -0.13 % h⁻¹. As seen from Figure 1 performance varies with MdAPEs on an individual basis ranging between 4.1% and 64.2%. Similar variability was found for the other performance metrics; MdPE (range): -25.6% to 64.2%, Wobble (range): 2.12 % to 30.3 % and Divergence (range): -4.43 % h⁻¹ to 0.68 % h⁻¹.

By combining the data from this study with the study previously published by our group (19), we were able to improve the PopPK model for cefepime. The following modifications led to a significant improvement in the goodness-of-fit: (i) the implementation of eCrCL as time-varying covariate on CL_{renal}, (Δ OFV: -75.3) and (ii) the addition of between-subject variability (BSV) on the non-renal CL (CL_{other}) (Δ OFV: -54.0). Finally, we made two modifications that slightly worsened goodness-of-fit: a power parameterization for the eCrCL effect on CL instead of the original linear relationship (Δ OFV: +2.2) and scaling of all PK parameters with body weight according to allometric theory (Δ OFV: +2.3) (20). The former was added to the model to avoid the prediction of negative CL_{renal} at very low eCrCL values whereas the latter was included to ascertain sensible behavior of a TCI system based on this model when used in patients with a bodyweight outside the range evaluated in this analysis (50 - 120 kg). None of the other covariates tested in the model (age, plasma albumin levels and C-reactive

120 protein (CRP)) were found significant. Parameter estimates and associated relative standard errors for the final
121 model are shown in Table 2. The covariate structure for the final model (for a non-dialysis patient) is shown in
122 equations 1-4. Goodness-of-fit plots for the final PopPK model are provided as supplemental material (Fig. S1).

$$123 \quad CL \text{ (L h}^{-1}\text{)} = \left(2.29 \cdot \left(\frac{eCrCL \text{ (mL min}^{-1}\text{)}}{60} \right)^{0.943} + 0.795 \right) \cdot \left(\frac{weight \text{ (kg)}}{70} \right)^{0.75} \quad \text{Eq.1}$$

$$124 \quad V1 \text{ (L)} = 10.7 \cdot \left(\frac{weight \text{ (kg)}}{70} \right)^1 \quad \text{Eq.2}$$

$$125 \quad V2 \text{ (L)} = 12.2 \cdot \left(\frac{weight \text{ (kg)}}{70} \right)^1 \quad \text{Eq.3}$$

$$126 \quad Q2 \text{ (L h}^{-1}\text{)} = 11.0 \cdot \left(\frac{weight \text{ (kg)}}{70} \right)^{0.75} \quad \text{Eq.4}$$

127

128

129 DISCUSSION

130 In this study we describe for the first time the use of TCI for the administration of antibiotics in
131 critically ill patients. PK-PD optimized dosing regimens and target attainment are pivotal for effective
132 antimicrobial treatment (4-5). As a result, different approaches to personalized antibiotic dosing have been
133 attempted (15,21-24). TCI systems accomplish this individualization *via* embedded PopPK models and might
134 therefore become a convenient bedside alternative to other approaches. Our prototype TCI system delivers
135 50.3% of measured cefepime concentrations within $\pm 30\%$ around the target value of 16 mg L^{-1} . MdPE and
136 MdAPE in this study were 20.3 % and 28.7 %, respectively. This performance is in line with the performance of
137 current PK models used in TCI pumps in anaesthesia (25).

138 Cefepime was selected as study drug because it is widely used as broad spectrum antibiotic in ICU
139 patients and individualized TCI dosing has a potential benefit given the relatively small therapeutic-toxic
140 window, compared to other beta-lactam antibiotics. It is important to note that there exist no clinically validated
141 target cefepime concentration for continuous infusion. We choose a target (total) cefepime concentration of 16
142 mg L^{-1} for all patients in our study, which is a compromise between potential toxicity and achieving adequate
143 PKPD targets. The chosen target concentration is well below the recently advocated threshold for cefepime
144 toxicity of 35 mg L^{-1} (6) and is sufficient to achieve free drug above the EUCAST clinical susceptibility
145 breakpoint for the suspected pathogens (e.g. MIC = 1 mg L^{-1} for *Enterobacterales* and MIC = 8 mg L^{-1} for
146 *Pseudomonas* spp.) (<http://www.eucast.org>). The target resembles the clinical use of cefepime when
147 microbiology results are absent, such as e.g. when used empirically or when cultures remain negative throughout
148 the treatment period (26,27). In these situations population-level assumptions are made about the most likely

149 organism causing the infection and the distribution of MICs in this population. To achieve true individualization
150 of antibiotic therapy, it might also be necessary to individualize the targeted PKPD index (i.e. more aggressive
151 PKPD targets such as $fT_{>2.1 \times \text{MIC}}$ (28) or $T_{>4.3 \times \text{MIC}}$ (29)) and to account for the susceptibility of the infecting
152 pathogen (once isolated). TCI systems facilitate the use of a patient-tailored target by reducing the complex
153 dose-concentration relationship *via* the embedded PopPK models to the selection of an appropriate plasma
154 concentration target. In our opinion, this practicable flexibility could drive the wide-spread implementation of
155 model-informed precision dosing for antibiotics in the ICU. The use of TCI is not limited to cefepime, but the
156 concept could also be applied to administer any drug that can be give as continuous infusion.

157 The additional PK data from this study enabled us to update the PopPK model used in our prototype
158 TCI system. From the pooled data analysis V1 was estimated to be 10.7 L and not 18.3 L, as published earlier by
159 our group (19). As a result, loading doses administered by the current version of the TCI system are too high,
160 resulting in an overshoot of the target in the first hour of treatment (as seen from Figure 1). Furthermore, our
161 analysis indicated that within-individual changes in cefepime clearance are (partly) explained by temporal
162 changes in eCrCL. We hypothesize that an updated version of the TCI system based on the new PopPK model
163 and with eCrCL as a control variable to accommodate within-subject variability in CL will perform better than
164 the system evaluated in this study.

165 The theoretical lower limit for the performance of this new system depends on the magnitude of the
166 unknown BSV in the PopPK model. When targeting a steady-state plasma concentration and assuming that the
167 PopPK model in the TCI system is unbiased, target attainment is limited by the BSV in CL. In our model CL
168 consists of CL_{renal} with a BSV of 24.6% and CL_{other} with a BSV of 69.4%. Consequently, when targeting 16 mg
169 L^{-1} 95% of patients are expected to reach a steady-state concentration between 9.16 and 24.6 mg L^{-1} (based on
170 simulations for a population with an average eCrCL of 60 mL min^{-1}). This translates to a MdAPE of 21.5%,
171 which is, as expected, lower than the MdAPE reported in this study (28.7%). This shows that it is possible to
172 improve the performance of the current TCI system by updating the embedded PopPK model.

173 Another useful approach for further refining the accuracy of the system is to use model-based feedback-
174 control based on Bayesian forecasting of PK parameters . Open-loop TCI systems (or adaptive TCI systems) (30)
175 where feedback from TDM is used as a control variable in the TCI system are interesting in that respect. Neely
176 *et al.* (21), Matthews *et al.* (23) and Pea *et al.* (24) have shown for aminoglycosides and vancomycin that TDM
177 and Bayesian forecasting of PK parameters results in improved dosing accuracy over conventional dosing
178 strategies. Hence, a TCI system based on the same principles might be advantageous when a higher accuracy is

179 needed. The lower limit for the performance of such a system is not depending on the BSV in the PK but is
180 governed by the residual variability of the PopPK model, which incorporates both the inaccuracy in the drug
181 assay and model misspecification. For the updated model this would result in a MdAPE of 12.8%. Nevertheless,
182 timely availability of appropriate antimicrobial assays could be problematic as TDM programs for cefepime or
183 other beta-lactam antibiotics are not yet widespread. To this end, biosensor technology could offer an alternative
184 by providing real-time monitoring of antimicrobials in a minimally invasive fashion (31).

185

186 There are some limitations to the research presented here: firstly, the small number of patients examined
187 and the fact that all patients originate from only one ICU site. Although patient inclusion was not restricted to
188 any medical condition and all patients receiving cefepime with a eGFR > 15 mL/min were eligible, extrapolation
189 of the results to specific subgroup of patients may not be appropriate. For instance, only few patients with
190 augmented renal clearance were included. Secondly, the model by Jonckheere *et al.* (19) uses only eCrCL to
191 individualize cefepime dosing. A more sophisticated PopPK model, also including patient covariates on the
192 volume of distribution, would have likely resulted in better treatment individualization and potentially better
193 performance. Finally, the TCI performance might be overestimated because the PopPK model which was
194 integrated in the TCI was developed in the same ICU.

195 In conclusion, novel systems are urgently required to individualize antimicrobial therapy, to address the
196 wide variations in PK currently observed across a range of patient populations, and to minimize the occurrence
197 of sub-optimal dosing. We demonstrated that cefepime TCI is able to deliver antibiotic concentrations within the
198 expected range around the targeted plasma concentrations in a cohort of critically ill ICU patients. In our
199 opinion, TCI offers exciting possibilities for the individualization of antibiotic treatment in ICU patients and
200 could drive the wide-spread implementation of model-informed precision dosing in this vulnerable patient
201 population. Further research is needed to confirm that target attainment is superior and to demonstrate increased
202 clinical efficacy in terms of clinical outcome. The role of TDM in an adaptive TCI approach also requires further
203 investigation.

204

205

206

207

208

209 MATERIALS AND METHODS

210 **Patient inclusion & research ethics.** Patients requiring cefepime according to local treatment protocols
211 were included between May 2016 and August 2017. Patients with an estimated glomerular filtration rate (eGFR)
212 (according to CKD-EPI formula) less than 15 mL/min and patients that were on hemodialysis were excluded.
213 This trial was conducted at the Intensive Care department of the OLV Hospital Aalst, Belgium, in accordance
214 with the Declaration of Helsinki and in compliance with Good Clinical Practice and the applicable regulatory
215 requirements. Ethical approval was obtained from the Institution Review Board of the hospital (Belgium
216 registration number: B126201626975). The study was registered in the ClinicalTrials.gov database
217 (NCT02688582) and was monitored by an independent Quality Specialist.

218 **Drug administration.** Patients received cefepime i.v. using a TCI system based on a previously
219 developed PopPK model by Jonckheere *et al.* (19). In this model, the estimated creatinine clearance (eCrCl)
220 based on the Cockcroft-Gault formula measured the day of inclusion was used as only input variable and a
221 cefepime blood concentration of 16 mg/L was targeted. There were no adaptations based on changes in eCrCl or
222 measured cefepime concentrations during treatment. Cefepime (20 mg/mL, Fresenius Kabi®, USA) was
223 administered by a syringe pump (Orchestra® Module DPS, Fresenius Kabi®, USA) controlled by RUGLOOPII
224 software (Demed®, Temse, Belgium) on a personal computer. Maximum infusion rate was set to 4 gram of
225 cefepime per hour.

226 **Descriptive statistics.** The administered daily cefepime dose was extracted from the case report forms
227 or the RUGLOOPII files. CRP measurements were summarized according to 24h intervals. Measurements up to
228 24h before inclusion into the study were grouped as baseline measurements. Daily doses of cefepime and CRP
229 levels were analysed for the first 4 days of therapy only, afterwards the number of patients treated was too low to
230 calculate meaningful summary measures. Length-of-stay in ICU/Hospital and mortality are competing risks (i.e.
231 very sick patients who die would have likely had a very long stay in ICU/Hospital), hence the length-of-stay was
232 calculated by replacing length-of-stay for patients who died by the maximum length-of-stay in that patient cohort
233 (32). Presence of neurotoxicity was based on clinical assessment.

234 **Arterial blood and urine sampling and laboratory procedures.** Arterial blood was sampled at 0.5, 1,
235 3, 6, 12, 24, 36, 48, 72, 96 and 120 h after the start of the infusion. The exact timing of blood samples was
236 recorded in the case report form. Samples were collected in lithium heparin tubes, transported immediately to the
237 laboratory and centrifuged at 1000 xg for 5 min at 4°C. Subsequently, plasma samples were stored below -70°C
238 until analysis. Urine was collected daily from a urinary catheter over a 12 hour interval. The quantification of

239 cefepime levels was based on a validated solid phase extraction – liquid chromatography electrospray – tandem
240 mass spectrometry method (33). using a $^{13}\text{C}_{12}$ - $^2\text{H}_3$ -labeled cefepime isotope as internal standard (AlsaChim,
241 Illkirch, France). The range of the analytical method was 0.15 mg L^{-1} to 15 mg L^{-1} with an average bias and
242 imprecision of +5.9 % and 8.6 CV%. Plasma samples were diluted 1/5 in blank human plasma whereas urine
243 samples were diluted 1/50 in blank human plasma prior to analysis. All samples were measured in duplicate.
244 Microbiological samples were taken as per standard of care and analyzed using standard culture procedures.
245 Identification was performed using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry
246 (MALDI-TOF MS) (Bruker Daltonik GmbH, Germany) and antimicrobial susceptibility testing was performed
247 using the Phoenix system (Becton Dickinson, USA) according manufacturer's instructions.

248 **Calculation of predictive performance.** In line with studies on the performance of TCI systems in
249 anesthesia, we used the “Varvel criteria” to evaluate the performance of our TCI system (34). For this, the
250 performance error (PE) is calculated for all samples (j) for the different patients (i) according to equation 5.

251

$$252 \quad PE_{ij} = \frac{(C_{meas\ ij} - C_{pred\ ij})}{C_{pred\ ij}} \times 100\% \quad \text{Eq 5.}$$

253

254 In this equation $C_{meas\ ij}$ and $C_{pred\ ij}$ are the measured and predicted plasma cefepime concentrations, respectively.
255 Subsequently, the PEs are used to calculate the median PE (MDPE), median absolute PE (MDAPE), wobble, and
256 divergence for each patient. MDPE provides a measure of bias whereas the MDAPE reflects the precision of the
257 system. Wobble is a measure of intra-subject variation in PEs and the divergence quantifies any time-related
258 changes in the imprecision of the TCI system.

259 **Update of previously published population pharmacokinetic model.** The plasma and urine cefepime
260 concentration versus time data were fitted using the FOCE-I estimation algorithm in NONMEM® (Version 7.3;
261 GloboMax LLC, Hanover, MD, USA). The “tidyverse” package (Version 1.1.1.; Wickham H. 2017) in R® (R
262 foundation for statistical computing, Vienna, Austria) was used to graphically assess the goodness-of-fit. As a
263 starting point, the model previously published by our group (19), which was used as PopPK model in the
264 presented TCI system, was fitted to the combined dataset (PK data from the pilot study (19) and additional PK
265 data from this TCI study). Modifications to the model were accepted if they resulted in a decrease in the
266 objective function value (OFV). A decrease in OFV was judged statistically significant if inclusion of an
267 additional parameter decreased the OFV with more than 3.84 points.

268

REFERENCES

1. Tam VH, Chang KT, Zhou J, Ledesma KR, Phe K, Gao S, Van Bambeke F, Sánchez-Díaz AM, Zamorano L, Oliver A, Cantón R. 2017. Determining β -lactam exposure threshold to suppress resistance development in Gram-negative bacteria. *J Antimicrob Chemother* 72:1421-1428.
2. Lamoth F, Buclin T, Pascual A, Vora S, Bolay S, Decosterd LA, Calandra T, Marchetti O. 2010. High cefepime plasma concentrations and neurological toxicity in febrile neutropenic patients with mild impairment of renal function. *Antimicrob Agents Chemother* 54:4360-4367.
3. Huwyler T, Lenggenhager L, Abbas M, Ing Lorenzini K, Hughes S, Huttner B, Karmime A, Uçkay I, von Dach E, Lescuyer P, Harbarth S, Huttner A. 2017. Cefepime plasma concentrations and clinical toxicity: a retrospective cohort study. *Clin Microbiol Infect* 23:454-459.
4. Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, Kaukonen KM, Koulenti D, Martin C, Montravers P, Rello J, Rhodes A, Starr T, Wallis SC, Lipman J; DALI Study. 2014. DALI: defining antibiotic levels in intensive care unit patients: are current β -lactam antibiotic doses sufficient for critically ill patients? *Clin Infect Dis* 58:1072-1083.
5. Abdul-Aziz MH, Lipman J, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, Dulhunty J, Kaukonen KM, Koulenti D, Martin C, Montravers P, Rello J, Rhodes A, Starr T, Wallis SC, Roberts JA; DALI Study Group. 2016. Is prolonged infusion of piperacillin/tazobactam and meropenem in critically ill patients associated with improved pharmacokinetic/pharmacodynamic and patient outcomes? An observation from the Defining Antibiotic Levels in Intensive care unit patients (DALI) cohort. *J Antimicrob Chemother* 71:196-207.
6. Payne LE, Gagnon DJ, Riker RR, Seder DB, Glisic EK, Morris JG, Fraser GL. 2017. Cefepime-induced neurotoxicity: a systematic review. *Crit Care* 21:276.
7. Uldemolins M, Roberts JA, Rello J, Paterson DL, Lipman J. 2011. The effects of hypoalbuminaemia on optimizing antibacterial dosing in critically ill patients. *Clin Pharmacokinet* 50:99-110.
8. Udy AA, Dulhunty JM, Roberts JA, Davis JS, Webb SAR, Bellomo R, Gomersall C, Shirwadkar C, Eastwood GM, Myburgh J, Paterson DL, Starr T, Paul SK, Lipman J; BLING-II Investigators; ANZICS Clinical Trials Group. 2017. Association between augmented renal clearance and clinical outcomes in patients receiving β -lactam antibiotic therapy by continuous or intermittent infusion: a nested cohort study of the BLING-II randomised, placebo-controlled, clinical trial. *Int J Antimicrob Agents* 49:624-630.

- 299 9. Roberts JA, Joynt GM, Choi GY, Gomersall CD, Lipman J. 2012. How to optimise antimicrobial
300 prescriptions in the intensive care unit: principles of individualized dosing using pharmacokinetics and
301 pharmacodynamics. *Int J Antimicrob Agents* 39:187–192.
- 302 10. Tsai D, Lipman J, Roberts JA. 2015. Pharmacokinetic/pharmacodynamic considerations for the
303 optimization of antimicrobial delivery in the critically ill. *Curr Opin Crit Care* 21:412–420.
- 304 11. Veiga RP, Paiva JA. 2018. Pharmacokinetics-pharmacodynamics issues relevant for the clinical use of
305 beta-lactam antibiotics in critically ill patients. *Crit Care* 22:233.
- 306 12. De Waele JJ, Akova M, Antonelli M, Canton R, Carlet J, De Backer D, Dimopoulos G, Garnacho-
307 Montero J, Kesecioglu J, Lipman J, Mer M, Paiva JA, Poljak M, Roberts JA, Rodriguez Bano J, Timsit
308 JF, Zahar JR, Bassetti M. 2018. Antimicrobial resistance and antibiotic stewardship programs in the
309 ICU: insistence and persistence in the fight against resistance. A position statement from
310 ESICM/ESCMID/WAAAR round table on multi-drug resistance. *Intensive Care Med* 44:189-196.
- 311 13. Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, Kaukonen KM, Koulenti D,
312 Martin C, Montravers P, Rello J, Rhodes A, Starr T, Wallis SC, Lipman J; DALI Study. 2014. DALI:
313 defining antibiotic levels in intensive care unit patients: are current β -lactam antibiotic doses sufficient
314 for critically ill patients? *Clin Infect Dis* 58:1072-1083.
- 315 14. Tasa T, Metsvaht T, Kalamees R, Vilo J, Lutsar I. 2017. DosOpt: a tool for personalized Bayesian dose
316 adjustment of vancomycin in neonates. *Ther Drug Monit* 39:604–613.
- 317 15. Felton TW, Roberts JA, Lodise TP, Van Guilder M, Boselli E, Neely MN, Hope WW. 2014.
318 Individualization of piperacillin dosing for critically ill patients: dosing software to optimize
319 antimicrobial therapy. *Antimicrob Agents Chemother* 58:4094-4102.
- 320 16. Wong G, Brinkman A, Benefield RJ, Carlier M, De Waele JJ, El Helali N, Frey O, Harbarth S, Huttner
321 A, McWhinney B, Misset B, Pea F, Preisenberger J, Roberts MS, Robertson TA, Roehr A, Sime FB,
322 Taccone FS, Ungerer JP, Lipman J, Roberts JA. 2014. An international, multicentre survey of β -lactam
323 antibiotic therapeutic drug monitoring practice in intensive care units. *J Antimicrob Chemother*
324 69:1416-1423.
- 325 17. Tabah A, De Waele J, Lipman J, Zahar JR, Cotta MO, Barton G, Timsit JF, Roberts JA; Working
326 Group for Antimicrobial Use in the ICU within the Infection Section of the European Society of
327 Intensive Care Medicine (ESICM). 2015. The ADMIN-ICU survey: a survey on antimicrobial dosing
328 and monitoring in ICUs. *J Antimicrob Chemother* 70:2671-2677.

- 329 18. Struys MMRF, De Smet T, Glen JI, Vereecke HE, Absalom AR, Schnider TW. 2016. The History of
330 Target-Controlled Infusion. *Anesth Analg* 122:56-69.
- 331 19. Jonckheere S, De Neve N, De Beenhouwer H, Berth M, Vermeulen A, Van Bocxlaer J, Colin P. 2016.
332 A model based analysis of the predictive performance of different renal function markers for cefepime
333 in the intensive care unit. *J Antimicrob Chemother* 71:2538-2546.
- 334 20. West GB, Brown JH, Enquist BJ. 1997. A general model for the origin of allometric scaling laws in
335 biology. *Science* 276:122-126.
- 336 21. Neely MN, Kato L, Youn G, Kraler L, Bayard D, van Guilder M, Schumitzky A, Yamada W, Jones B,
337 Minejima E. 2018. Prospective trial on the use of trough concentration versus area under the curve to
338 determine therapeutic vancomycin dosing. *Antimicrob Agents Chemother* 62:e02042-17.
- 339 22. De Waele JJ, Carrette S, Carlier M, Stove V, Boelens J, Claeys G, Leroux-Roels I, Hoste E, Depuydt P,
340 Decruyenaere J, Verstraete AG. 2014. Therapeutic drug monitoring-based dose optimisation of
341 piperacillin and meropenem: a randomised controlled trial. *Intensive Care Med* 40:380-387.
- 342 23. Matthews I, Kirkpatrick C, Holford N. 2004. Quantitative justification for target concentration
343 intervention–parameter variability and predictive performance using population pharmacokinetic
344 models for aminoglycosides. *Br J Clin Pharmacol* 58:18-19.
- 345 24. Pea F, Furlanut M, Negri C, Pavan F, Crapis M, Cristini F, Viale P. 2009. Prospectively validated
346 dosing nomograms for maximizing the pharmacodynamics of vancomycin administered by continuous
347 infusion in critically ill patients. *Antimicrob Agents Chemother* 53:1863-1867.
- 348 25. Glass PS, Shafer S, Reves JG. 2005. Intravenous Drug Delivery Systems. In: Miller R (ed) *Miller's*
349 *Anesthesia*, 1. 6 edn. Elsevier, Philadelphia, PA, USA, pp 439-480.
- 350 26. Phua J, Ngerng W, See K, Tay C, Kiong T, Lim H, Chew M, Yip H, Tan A, Khalizah H, Capistrano R,
351 Lee K, Mukhopadhyay A. 2013. Characteristics and outcomes of culture negative versus culture-
352 positive severe sepsis. *Crit Care* 17: R202.
- 353 27. Zarb P, Goossens H. 2011. European Surveillance of Antimicrobial Consumption (ESAC): value of a
354 point-prevalence survey of antimicrobial use across Europe. *Drugs* 71:745–755.
- 355 28. Aitken SL, Altshuler J, Guervil DJ, Hirsch EB, Ostrosky-Zeichner LL, Ericsson CD, Tam VH. 2015.
356 Cefepime free minimum concentration to minimum inhibitory concentration (fCmin/MIC) ratio predicts
357 clinical failure in patients with Gram-negative bacterial pneumonia. *Int J Antimicrob Agents* 45:541–
358 544.

- 359 29. Tam VH, McKinnon PS, Akins RL, Rybak MJ, Drusano GL. 2002. Pharmacodynamics of cefepime in
360 patients with Gram-negative infections. *J Antimicrob Chemother* 50:425–428.
- 361 30. Colin PJ, Jonckheere S, Struys MMRF. 2018. Target-controlled continuous infusion for antibiotic
362 dosing: Proof-of-principle in an in silico vancomycin trial in intensive care patients. *Clin*
363 *Pharmacokinet* 57:1435-1447.
- 364 31. Rawson TM, O'Hare D, Herrero P, Sharma S, Moore LSP, de Barra E, Roberts JA, Gordon AC, Hope
365 W, Georgiou P, Cass AEG, Holmes AH. 2018. Delivering precision antimicrobial therapy through
366 closed-loop control systems. *J Antimicrob Chemother* 73:835-843.
- 367 32. Brock GN, Barnes C, Ramirez JA, Myers J. 2011. How to handle mortality when investigating length of
368 hospital stay and time to clinical stability. *BMC Med Res Methodol* 11:144.
- 369 33. Colin P, De Bock L, T'jollyn H, Boussery K, Van Bocxlaer J. 2013. Development and validation of a
370 fast and uniform approach to quantify b-lactam antibiotics in human plasma by solid phase extraction-
371 liquid chromatography-electrospray-tandem mass spectrometry. *Talanta* 103:285-293.
- 372 34. Varvel JR, Donoho DL, Shafer SL. 1992. Measuring the predictive performance of computer-controlled
373 infusion pumps. *J Pharmacokinet Biopharm* 20:63–94.

374
375
376
377
378
379
380
381
382
383
384
385
386
387
388

389 COI: Michel M. R. F. Struys and Ghent University have a financial interest in RUGLOOP II, a software
390 program for target-controlled infusion. His research group/department received grants and funding from The
391 Medicines Company (Parsippany, NJ, USA), Masimo (Irvine, CA, USA), Fresenius (Bad Homburg, Germany),
392 Acacia Design (Maastricht, The Netherlands), Medtronic (Dublin, Ireland), Paion (Aachen, Germany), PRA
393 (Groningen, The Netherlands) and honoraria from The Medicines Company (Parsippany, NJ, USA), Masimo
394 (Irvine, CA, USA), Fresenius (Bad Homburg, Germany), Baxter (Deerfield, IL, USA), Medtronic (Dublin,
395 Ireland), Becton Dickinson (San Diego, CA, USA) and Demed Medical (Temse, Belgium).

396 All other authors: none to declare.

397

398 Funding: This study was supported by internal funding.

399

400

401

402

403

404

405

406

407

408

409

410

411

412

413

414

415

416 **FIGURE LEGENDS**

417 **FIG 1** Measured cefepime concentrations (black dots) with non-parametric smoother (blue line) and target
418 window of 16 mg/L of the 21 included patients. Black line represents expected plasma concentrations based on
419 TCI model. Median absolute prediction error (MdAPE) is presented for each patient.

Table 1 Clinical characteristics of study patients (n=21).

Clinical outcome	<i>n</i> (%) or median (IQR)
Age	76 (72 – 78)
Male/female	16 (76) / 5 (24)
Body weight (kg)	76 (67 – 86)
BMI (kg/m ²)	26.3 (23.5 – 27.8)
Body surface area (m ²)	1.88 (1.77 – 2.03)
SOFA score at inclusion	7 (3 – 8)
Patients on mechanical ventilation at inclusion	7 (33)
Serum creatinine (mg/dL)	1.49 (0.66 – 2.14)
Cockcroft-Gault (mL/min)	50.4 (29.1 – 100)
MDRD (mL/min/1.73 m ²)	42.3 (30.1 – 106)
CKD-EPI (mL/min/1.73 m ²)	38.8 (26.8 – 83.3)
CRP (mg L ⁻¹)	
At study inclusion	197 (95.7 – 287)
0 – 24 h	189 (115 – 282)
24 – 48 h	133 (92.6 – 195)
48 – 72 h	89.2 (62.5 – 122)
72 – 96 h	69.0 (46.7 – 88)
Length of stay in ICU (days) ^a	7 (5 – 10)
Length of stay in hospital (days) ^a	21 (13 – 28)
In hospital mortality	5 (24)
Event of neurotoxicity	0 (0)

^amortality-corrected length of stay

Table 2 Parameter estimates and associated relative standard errors (RSE%) for the final population PK model derived from simultaneously fitting the data from our previous study (19) (STDY1) and the data from this study (STDY2). Between-subject variability associated with the typical parameters is expressed as CV%. eCrCL was according to Cockcroft-Gault and was interpolated using constant backward interpolation.

PK Parameter	Estimate (RSE %)
CL _{renal} (L h ⁻¹ 70 kg ⁻¹)	$\theta_1 \cdot \left(\frac{eCrCL (mL \cdot min^{-1})}{60} \right)^{\theta_2}$
θ_1	2.29 (5.4)
θ_2	0.943 (9.6)
CL _{other} (L h ⁻¹ 70 kg ⁻¹)	0.795 (9.0)
V1 (L 70 kg ⁻¹)	10.7 (8.1)
V2 (L 70 kg ⁻¹)	12.2 (7.2)
Q2 (L h ⁻¹ 70 kg ⁻¹)	11.0 (14)
CL _{dialysis} (L h ⁻¹)	4.48 (8.1)
Between-subject variability (CV%^a)	
CL _{renal}	24.6 (28)
V1	45.7 (31)
CL _{other}	69.4 (32)
Residual unexplained variability (CV%)	
Plasma _{STDY1}	31.8 (17)
Plasma _{STDY2}	12.8 (25)
Urine _{STDY1}	32.5 (27)
Urine _{STDY2}	33.3 (42)

V1, volume of distribution of the central compartment; V2, volume of distribution of the peripheral compartment; Q2, inter-compartmental clearance between V1 and V2; CL_{renal}, renal clearance; CL_{dialysis}, clearance during intermittent haemodialysis; CL_{other}, non-renal clearance. Separate clearance terms are integrated in the model describing renal clearance, non-renal clearance and clearance during haemodialysis. For patients on IHD, we assumed that renal clearance was absent.

^a CV (%) is calculated according to: $\sqrt{\omega^2} \cdot 100\%$ where ω^2 is the estimated variance in NONMEM

